

REMARKS

Favorable reconsideration of this application in view of the remarks to follow and allowance of the claims of the present application are respectfully requested.

In the Official Action, Claim 1 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Official Action avers that applicant's addition of "to those patients whose CYP3A levels indicate formation of a metabolite of nemorubicin more active than nemorubicin" in Claim 1 is new matter. In response to the applicants' assertion (included in the response submitted on April 4, 2008) that the above-identified addition is taught in the instant specification (see page 2, lines 9-15), the Official Action contends that the specification merely teaches that there is a metabolite of nemorubicin which is more cytotoxic than nemorubicin, when broken down in the liver, however it does not say anything about CYP3A being the enzyme, or that explain how that CYP3A levels would indicate the presence of this more active metabolite. Therefore, the Official Action concludes that this new addition presents a new idea which wasn't presented in the original application and is thus new matter.

In response, applicants respectfully submit that this is not the case. Specifically, applicants submit that the instant specification provides an experimental section (see page 2, line 20 to page 4, line 13) where it describes that the experimental results "showed that only CYP3A4 isoenzyme is responsible for the metabolism of nemorubicin." See page 3, lines 30-32. Moreover, the instant specification provides that "[t]he metabolism of nemorubicin correlates with the levels of CYP3A in human liver samples. More specifically there was a strict correlation only with the expression of CYP3A enzymatic activity and not with other CYP isoenzymes...." See page 3, lines 25-27.

In view of the above remarks, applicants submit that the specification clearly describes that the CYP3A is the enzyme responsible for the metabolism of nemorubicin, and the CYP3A levels correlate with metabolites of nemorubicin which, by common sense, include the more active metabolite of nemorubicin. As such, applicants respectfully submit that the instant §112, first paragraph rejection has been obviated, and reconsideration and withdrawal of the same is respectfully requested.

Furthermore, Claims 1, 3, 5, 7 and 11-14 stand rejected, under 35 U.S.C. §103(a), as allegedly unpatentable over Collins et al., *Clin. Cancer Res.*, 6:1203-1204, 2000 ("Collins et al.") in view of Beulz-Riché et al., *Cancer Chem. Pharm.*, 49:274-280, 2002 ("Beulz-Riché et al."), and in further view of Pacciarini et al., WO 00/15203 ("Pacciarini et al.").

Specifically, the Official Action contends that Collins et al. teach using ERMBT as a way to individualize doses of an anticancer drug docetaxel, which is metabolized by CYP3A (see page 1203, first paragraph). Although Collins et al. does not teach nemorubicin, Beulz-Riché et al. teaches that nemorubicin (also known as MMDX or methoxymorpholinodoxorubicin) is metabolized by CYP3A. Although neither reference mentions the treatment of liver cancer, Pacciarini et al. teaches that methoxymorpholino doxorubicin (nemorubicin) is useful for treatment of liver cancer. Pacciarini et al. further teaches that MMDX is more potent when administered *in vivo*, and that the cytotoxic activity of MMDX is increased in the presence of liver microsomes, suggesting that MMDX may be transformed into highly cytotoxic metabolites. Therefore, the Official Action alleges that it would have been obvious for a person skilled in the art to substitute MMDX for docetaxel in the ERMBT test to determine the amount metabolized in order to individualize dosages for liver cancer treatment.

In response, applicants submit that reliance on Collins et al. is inappropriate in assessing the results achieved by the claimed method. In this regard, applicants submit that the effectiveness of a method of individualizing doses of an anticancer drug according to the levels of the metabolizing enzyme of the same drug which indicates formation of a more active metabolite than the parent drug, depends on the type of the anticancer drug, the nature of the metabolite of the same drug, and the intended mechanism of the treatment. If the type of the anticancer drug, the nature of the metabolite and the intended mechanism of treatment are different from one art to another, one skilled in the art would be unable to utilize the same method as in the prior art to effect the intended method. In other words, the type of methodology utilized is dependent upon each set of circumstances and cannot be generalized.

In this regard, applicants would like to draw the Examiner's attention to the fact that the type of the anticancer drug, the nature of the metabolite and the intended mechanism of treatment disclosed in Collins et al. are different from that of the present invention.

Specifically, the type of anticancer drug disclosed in Collins et al. is docetaxel, which is structurally and functionally different from nemorubicin as presently claimed. Moreover, with respect to the nature of the metabolite of the drug, the metabolite of docetaxel, as disclosed in Collins et al., is inactive, and thus is then excreted by the human body. In contrast, the metabolite of nemorubicin, as presently claimed, is more active than nemorubicin, and thus is effective in the treatment of the diseases. Furthermore, regarding the intended mechanism of treatment contemplated by the method, Collins et al. teaches a method where the mechanism of treatment is to ascertain CYP3A levels in order to avoid those patients having a too rapid elimination of docetaxel. In other words, Collins et al. teaches a method of eliminating patients for whom treatment with docetaxel would be futile, due to its rapid metabolism by CYP3A in the

liver. In fundamental contrast, the presently claimed method is concerned with the evaluation of CYP3A levels which is aimed at selecting those patients that will be more responsive to the nemorubicin treatment. In other words, the presently claimed method is to identify patients who would benefit when treatment with nemorubicin is provided. Therefore, although docetaxel and nemorubicin are metabolized by CYP3A, the therapeutic effect is completely different owing the different properties of the resulting metabolites. That is, the docetaxel metabolite is inactive, so, in case of high levels of CYP3A, the treatment is less effective.

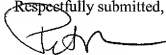
In view of the above remarks, together with the unpredictable nature of cancer treatment, applicants submit that a person skilled in the art would not apply Collins et al. in arriving at the present invention because Collins et al. is inapplicable to assess the results achieved by the claimed method for the reasons explained above.

Furthermore, even assuming *pro arguendo* that Collins et al. would be applicable to the present invention, which is clearly not the case as discussed above, applicants submit that the teaching from the combination of the cited references would not arrive at the present invention. Specifically, the combined references, at best disclose, that for a patient receiving nemorubicin, if the CYP3A level is high, then such patient should be eliminated from the treatment, and if the CYP3A level is low, then such patient should have a better response to the treatment, which is directly opposite to the present invention where high CYP3A levels suggest that the patient would receive more benefit from the treatment whereas low CYP3A levels indicate less benefit.

In view of the above remarks, applicants submit that the instant §103(a) rejection has been obviated. Reconsideration and withdrawal of the instant rejection is respectfully requested.

Thus, in view of the foregoing remarks, it is firmly believed that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Peter I. Bernstein', written over the typed name.

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